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PEPTIDES, STRUCTURE AND FUNCTION, Proc. of the 9th Am. Peptide Symp., Toronto, June 1985, pages 4615-4625; Pierce Chem. Co., Rockford, US, B.E. EVANS et al.: "A stereocontrolled synthesis of hydroxyethylene dipeptide isosteres using novel, chrial aminoalkyl epoxides; new renin inhibitor analogs"

J.MED. CHEM., vol. 26, 1983, pages 1457-1462; Am. Chem. Soc., US R.L. JOHNSON et al.: "Inhibition of renin by angiotensinogen peptide fragments containing the hydroxy amino acid residue 5-amino-3-hydroxy-7-methyloctanoic acid"

J.ORG. CHEM., vol. 45, 1980, pages 28-29; Am. Soc., US, M.M. MIDLAND et al.: "Synthesis of alkyl 4-hydroxy-2-alkynoates"

ANGEW. CHEM., Int. Ed. Engl., vol. 23, no. 2, 1984, pages 143-145; Verlag Chemie GmbH, Weinheim, DE, H-J. GAIS: "Stereoselective synthesis of (E)-4-hydroxy-2-alkenoic acid esters form aldehydes and the d3-building block ethyl lithiopropiolate"

Description

The present invention is concerned with intermediates useful for making peptide derivatives containing 5-amino-2,5-disubstituted-4-hydroxypentanoic acid residues, which are useful for inhibiting the angiotensinogen-cleaving action of the enzyme renin.

The proteolytic enzyme renin, which has a molecular weight of about 40,000, is produced in and secreted into the blood by the kidney. It is known to be active in vivo in cleaving the naturally-occurring plasma glycoprotein angiotensinogen. In the case of human angiotensinogen, cleavage is at the bond between the leucine (10th) and valine (11th) amino acid residues at the N-terminal end of the angiotensinogen:

```
Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-His-Leu-Val-
 1   2   3   4   5   6   7   8   9  10  11
                                Ile-His-Ser-Glu-
                               12  13  14  15
```

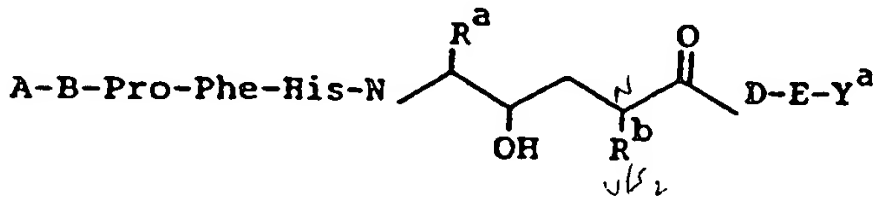
The circulating N-terminal decapeptide (angiotensin I) formed by the above cleaving action of renin is subsequently broken down by the body to an octapeptide known as angiotensin II. Angiotensin II is known to be a potent pressor substance, i.e. a substance that is capable of inducing a significant increase in blood pressure, and is believed to act by causing the constriction of blood vessels and the release of the sodium-retaining hormone aldosterone from the adrenal gland. Thus, the renin-angiotensinogen system has been implicated as a causative factor in certain forms of hypertension.

One means of alleviating the adverse effects of the functioning of the renin-angiotensinogen system is the administration of a substance capable of inhibiting the angiotensinogen-cleaving action of renin. A number of such substances are known, including antirenin antibodies, pepstatin and naturally-occurring phospholipid compounds. European Patent Application No. 77,028 discloses a series of renin-inhibiting polypeptide compounds having a non-terminal statine (Sta; 4-amino-3-hydroxy-6-methylheptanoic acid) or statine derivative. Including Sta, the vast majority of compounds exemplified contain 6 or more aminoacid residues. Exemplary of the few shortest chains there disclosed are:

Acetyl-Phe-His-Sta-Leu-Phe-NH_2, and

t-Butyloxycarbonyl-Phe-His-Sta-Leu-Phe-NH_2. There are invariably at least two amino acid residues each side of statine. The di- or polypeptidyl-statyl group is invariably attached to a lipophilic amino acid, most often leucine. (See also U.S. Patents 4,470,971 and 4,478,826).

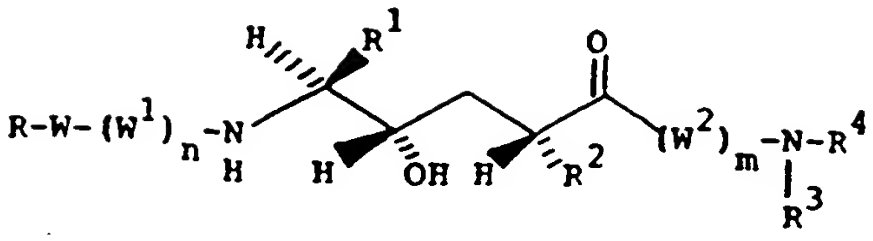
European Patent Application No. 45,665 and U.S. Patent 4,424,207 disclose a series of renin-inhibiting polypeptide derivatives of the formula:



where A is for example t-butoxycarbonyl, B is His or other basic aminoacyl group, D is Val, Ile or other liphophilic aminoacyl residue, E is Tyr, Phe, His or other aromatic aminoacyl residue, R^a and R^b are each isopropyl, isobutyl, benzyl or other lipophilic amino-acid type sidechain, and Y^a is a terminal acid, ester or amide type group. Including the central 5-aminopentanoic acid residues, these compounds are invariably heptapeptides, i.e., N-tetrapeptidyl-5-aminopentanoyl-lipophilic aminoacyl-aromatic amino-acid derivatives.

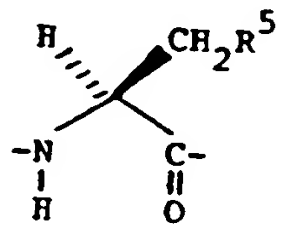
The article "Pept. Struct. Funct.", Proc. 9th Am. Pept. Symp. 4615-4625 (1985) describes a stereocontrolled 6-step synthesis of hydroxyethylene dipeptide isosteres from chiral aminoalkyl epoxides. J. Org. Chem. 45 28-29 (1980) and J. Med. Chem. 26 1457-1462 (1983) describe the addition of organic lithium compounds to aldehydes to produce racemic mixtures of alcohols.

Certain compounds possess exceptional value as renin-inhibiting agents. These compounds are peptide derivatives of the formula:

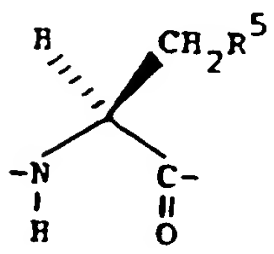


---(I)

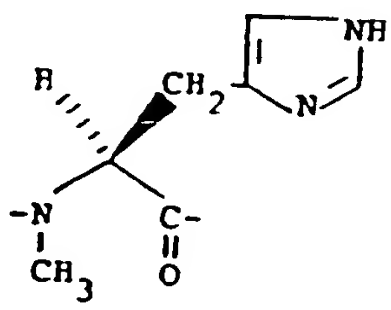
or a pharmaceutically acceptable salt thereof, wherein
n and m are each 1 or 0, the sum of n and m being at least 1;
W is



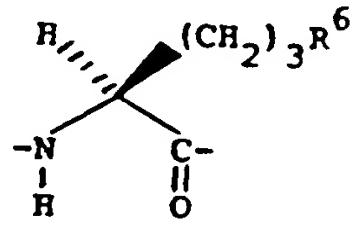
wherein R^5 is phenyl, 1-naphthyl, 4-hydroxyphenyl, 4-methoxyphenyl, 4-imidazolyl, propyl or isopropyl;
W^1 is



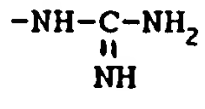
or



W^2 is



where R^6 is $-NH_2$,

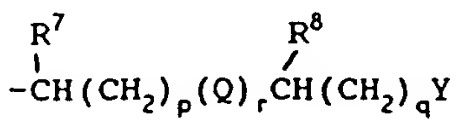


or $-CH_2NH_2$;
when n is 1, R is hydrogen, an amino-protecting acyl moiety having a molecular weight of less than 500, prolyl, pyroglytamyl, or prolyl or pyroglutamyl protected on nitrogen with said amino-protecting acyl

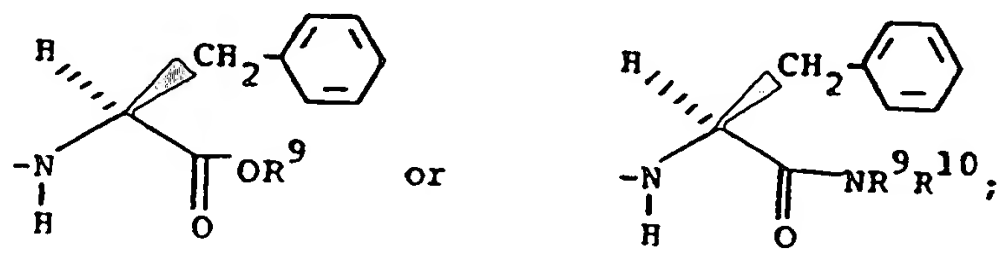
moiety; and when n is 0, R is phenoxyacetyl or 2-benzyl-3-phenylpropionyl (dibenzylacetyl);

R^1 and R^2 are each independently hydrogen, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkenyl, phenyl, naphthyl, $(C_4\text{-}C_7)$-cycloalkyl, $(C_4\text{-}C_7)$cycloalkenyl, $(C_7\text{-}C_9)$phenylalkyl, $(C_{11}\text{-}C_{13})$naphthylalkyl, $(C_5\text{-}C_{10}$(cycloalkyl)-alkyl, $(C_5\text{-}C_{10})$(cycloalkenyl)alkyl, or one of said groups mono- or disubstituted on the aromatic ring with the same or different groups selected from $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$alkoxy, fluoro or chloro; and

(a) R^3 and R^4 are taken separately, and are each independently hydrogen, $(C_1\text{-}C_6)$alkyl, phenyl, naphthyl, $(C_4\text{-}C_7)$cycloalkyl, adamantyl, $(C_7\text{-}C_7)$phenylalkyl, $(C_{11}\text{-}C_{13})$naphthylalkyl, $(C_5\text{-}C_{10})$(cycloalkyl)-alkyl or adamantyl; or R^3 is hydrogen and R^4 is

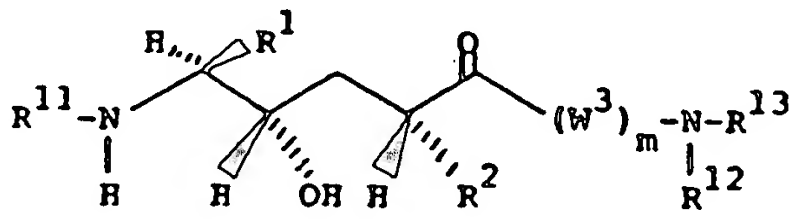


p and q are each independently zero or an integer from 1 to 6;
r is 0 or 1;
Q is $-CH_2-$, $-CH=CH-$, $-O-$, $-NH-$, $-CHOH-$ or $-CO-$;
Y is methyl, phenyl, $-COOR^9$, $-CONR^9R^{10}$, $-CONHCOOCH_2C_6H_5$, NH_2, $-NHCOCH_2C_6H_5$,



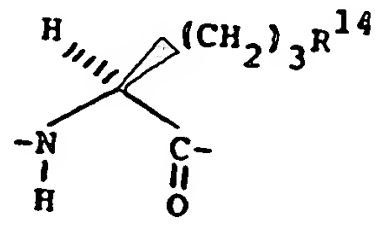
and R^7, R^8, R^9 and R^{10} are each independently hydrogen, $(C_1\text{-}C_6)$alkyl, phenyl, $(C_4\text{-}C_7)$cycloalkyl, $(C_7\text{-}C_9)$phenylalkyl, $(C_5\text{-}C_{10})$(cycloalkyl)alkyl, or adamantyl;
or
(b) R^3 and R^4 are taken together with the nitrogen to which they are attached to form a pyrrole, indoline, isoindoline, piperidine, 1,2,3,4-tetrahydroquinoline, 1,2,3,4-tetrahydroisoquinoline, perhydroazepine, or morpholine ring system.

The above-mentioned peptides may be made using intermediate compounds of the formula:

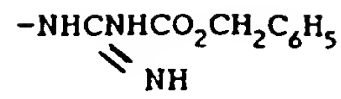


--(II)

wherein
R^1 and R^2 are as defined above;
W^3 is



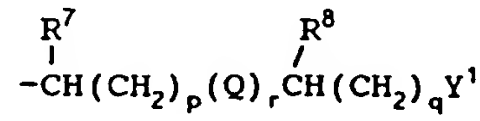
where R^{14} is $-NHCO_2CH_2CH_2C_6H_5$,



or $-CH_2NHCO_2C_6H_5$;

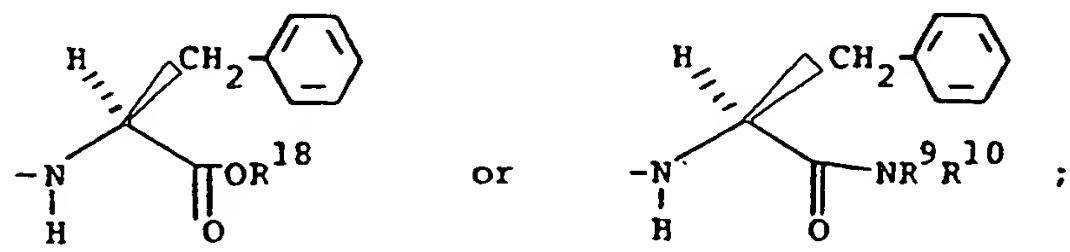
R^{11} is hydrogen or t-butoxycarbonyl; and

(a) R^{12} and R^{13} are taken separately and are each independently hydrogen, (C_1-C_6)alkyl, phenyl, naphthyl, (C_4-C_7)cycloalkyl, adamantyl, (C_7-C_9)phenylalkyl, $(C_{11}-C_{13})$naphthylalkyl or (C_5-C_{10})-(cycloalkyl)alkyl, or R^{12} is hydrogen and R^{13} is



p, q, r and Q are as defined above;

Y^1 is methyl, phenyl, $-COOR^{18}$, $-CONR^9R^{10}$, $-CONHCOOCH_2C_6H_5$, $-NHCOCH_2C_6H_5$,

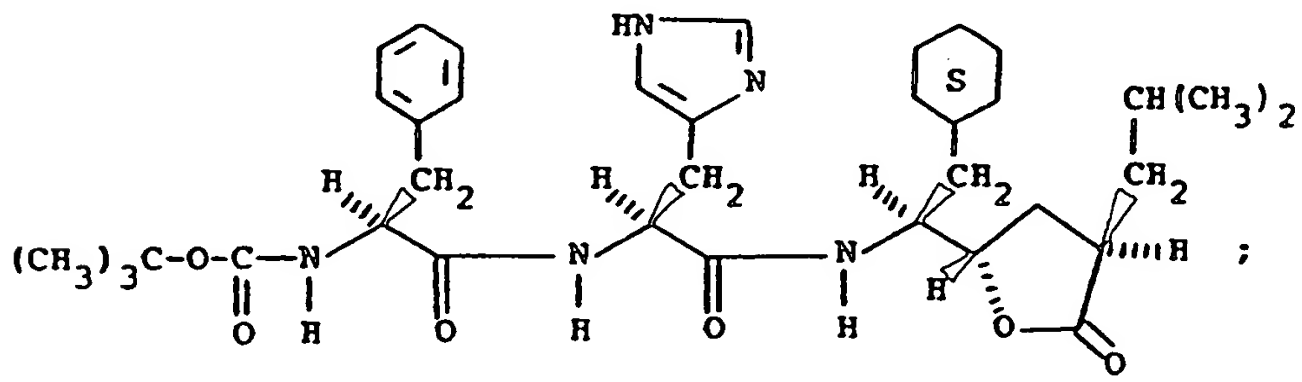


R^7, R^8, R^9 and R^{10} are each independently as defined above; and

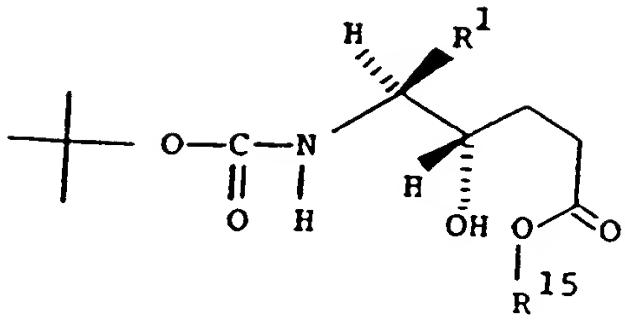
R^{18} is an independent value of R^7 other than hydrogen; or

(b) R^{12} and R^{13} are taken together with the nitrogen to which they are attached to form a pyrrole, indoline, isoindoline, piperidine, 1,2,3,4-tetrahydroquinoline, 1,2,3,4-tetrahydroisoquinoline, perhydroazepine, or morpholine ring system; and

an intermediate compound of the formula

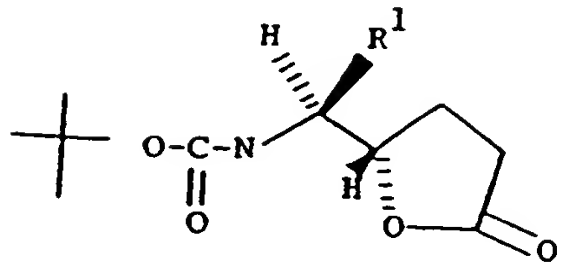


The present invention relates to the following compounds (III) and (IV) which are useful for making the above-mentioned intermediates;



(III)

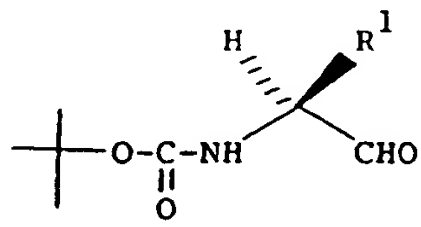
or



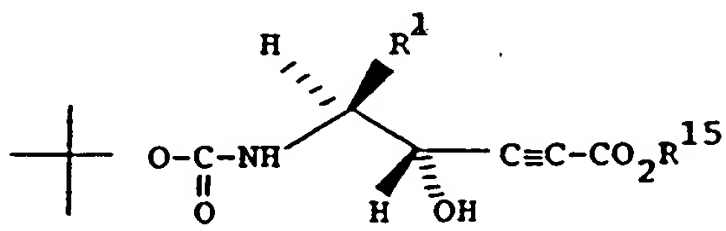
(IV)

wherein R^1 is as defined above but is other than hydrogen.

The invention also relates to a stereo-selective process for making the compound of formula (III) which comprises reacting an aldehyde of formula:

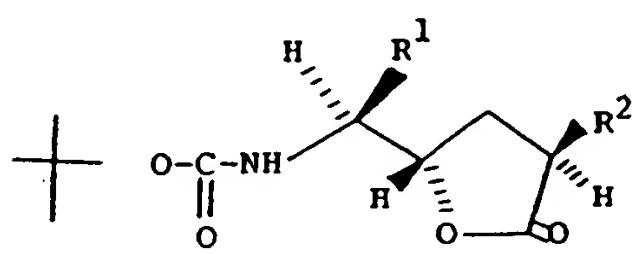


with $LiC{\equiv}CCOOR^{15}$, where R^{15} is $(C_1\text{-}C_3)$alkyl in a reaction-inert solvent at -50°C to -80°C to form a compound of formula:



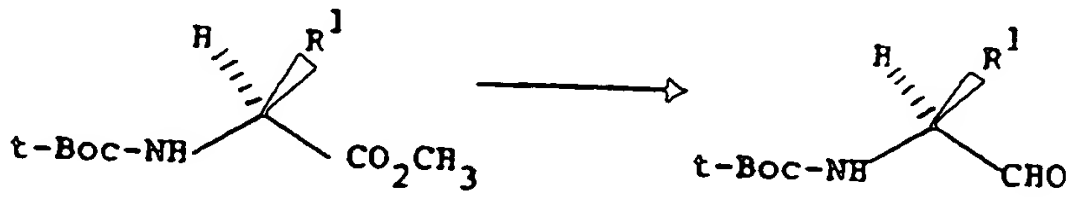
This compound may be hydrogenated to yield a compound of formula (III) which may then be cyclised to yield a compound of formula (IV).

The invention also relates to a stereoselective process for the preparation of a compound of formula:

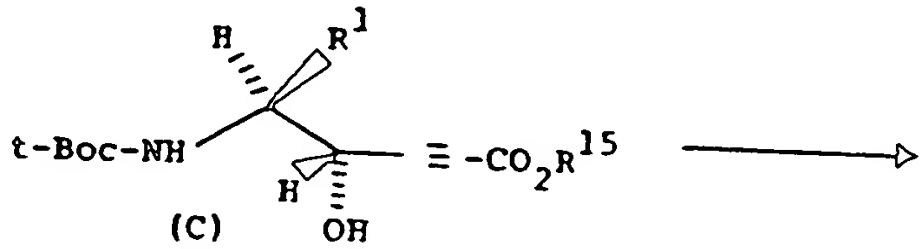


wherein R^1 is defined above and R^2 is (C_1-C_6)(2-alkenyl), (C_4-C_7)(cyclo-2-alkenyl), benzyl or naphthyl or one of these groups mono- or di-substituted on an aromatic with the same or different substituents which are (C_1-C_3)alkyl, (C_1-C_3)alkoxy, fluoro or chloro; which comprises reacting a lactone of formula (IV) above with substantially one molar equivalent of an organic halide of formula R^2X where X is Cl, Br or I in the presence of a strong base of low nucleophilicity. R^2 is preferably an activating allyl or benzyl type group. X is preferably Br.

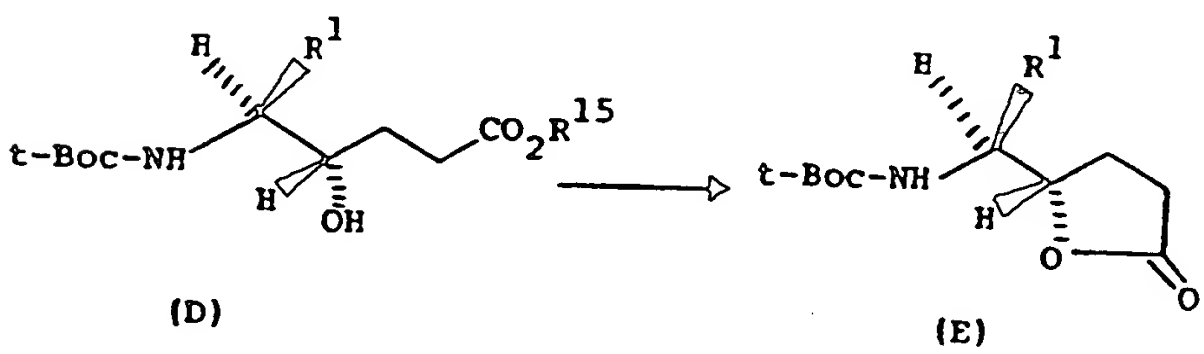
The above-mentioned reactions are illustrated as follows.



(A) (B)



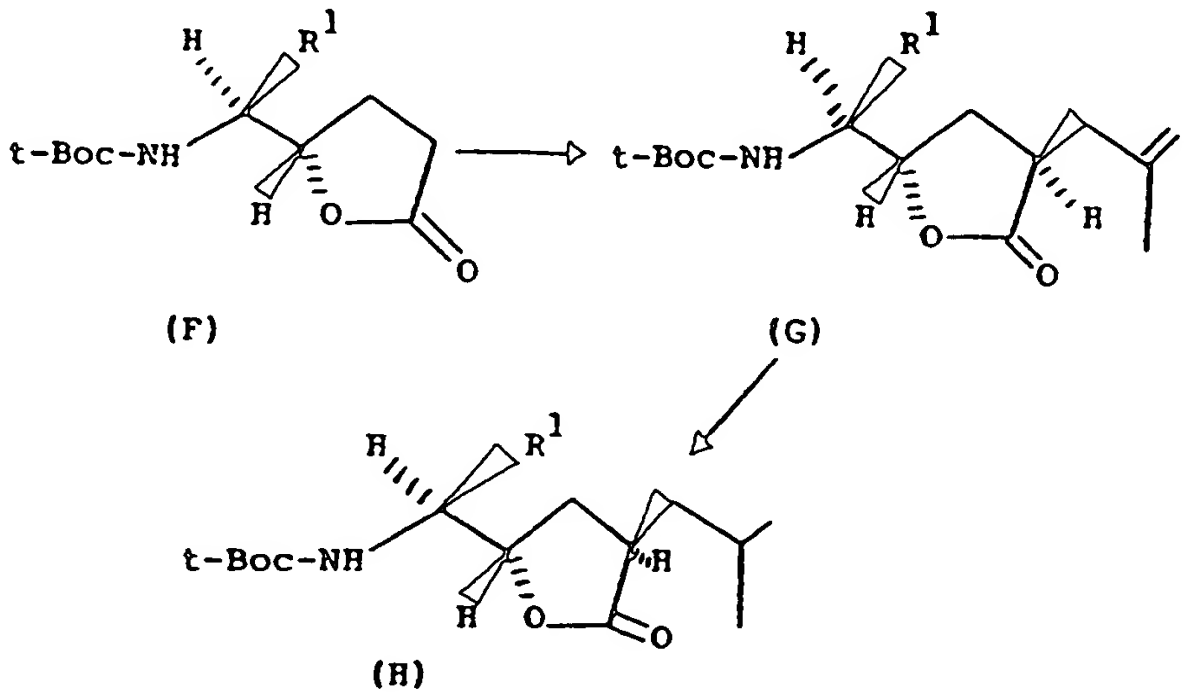
(C)



(D) (E)

The starting protected L-amino acid is obtained commercially or by standard methods well known in the art, including, when desired, reduction of an aromatic ring, e.g. that of N-(t-butoxycarbonyl)phenylalanine methyl ester as exemplified below. The lower alkyl ester, preferably the methyl ester as shown is readily reduced to the aldehyde, for example, with diisobutylaluminium hydride in toluene at -50 to -80 °C. The aldehyde in turn is reacted with $LiC{\equiv}CCOOR^{15}$ (usually R^{15} is ethyl formed in situ from ethyl propiolate), again at -50 to -80 °C., in a reaction inert solvent such as tetrahydrofuran. A pair of diastereoisomers are generally formed at this stage, with the desired diastereoisomer (C) greatly predominating. The lesser, undesired isomer is preferably removed following hydrogenation of the triple bond (carried out under standard hydrogenation conditions, e.g., over a palladium catalyst, preferably Pd in $BaSO_4$ under relatively mild conditions; and formation of the lactone (e.g., by reacting in toluene in the presence of acetic acid).

The desired lactone epimer, having the 4S stereo-chemistry shown in formula (E) and (F), is then condensed with a halide, R^2X (X = Cl, Br or I; preferably X = Br) in the presence of a substantial excess, e.g., 2 to 2.5 molar equivalents of a strong base of low nucleophilicity, such as $LiN[CH(CH_3)]_2$ or preferably, lithium hexamethyldisilazide. Preferably the halide is an allylic or benzylic type halide (e.g., 2-methyl-2-propenyl bromide, benzyl bromide) with the double bond or aromatic ring subsequently hydrogenated if the saturated group R^2 is desired, e.g.,



Once again, the desired diastereoisomer, having trans (2R) stereochemistry as shown, predominates. It is separated by chromatography (before or after any required hydrogenation to produce the desired group R^2). Alternatively, hydrogenation, particularly when R^2 at the stage of condensation is a benzyl group, can be deferred until latter in the overrall synthesis of the desired compound. The preferred catalysts for hydrogenation of a simple olefin comprise Pd or Rh, while for reduction of phenyl to cyclohexyl, Rh is preferred.

All structural designations of stereochemistry shown herein represent absolute stereochemistry. The present invention is illustrated by the following examples. However, it should be understood that the invention is not limited to the details of these examples. All temperatures are in °C. and are ambient unless otherwise specified. All stripping of solvents was in vacuo. All standard solutions are in water unless otherwise specified. THF stands for tetrahydrofuran.

EXAMPLE 1

S-3-Cyclohexyl-2-(t-butoxycarbonylamino)propionaldehyde

Methyl S-3-cyclohexyl-2-(t-butoxycarbonylamino)propionate (51.2 g., 0.179 mol) was dissolved in 728 ml. of dry toluene and cooled to -78°. Diisobutylaluminium hydride (449 ml. of 1M in toluene, 0.449 mol) was added dropwise over 1 hour, maintaining -70°C to -78°C. Methanol (13 ml.) was added at -70°, followed by 608 ml. of half-saturated sodium potassium tartrate, and the mixture warmed to ambient temperature. Ether (300 ml.) was added and the organic layer was separated and washed with 1 l. saturated sodium potassium tartrate. The original aqueous layer was extracted with 600 ml. fresh ether and backwashed with 600 ml. fresh saturated sodium potassium tartrate. The organic layers were combined, dried over $MgSO_4$ and stripped to yield title product as a gum, contaminated with toluene on the basis of ^{1}H-nmr, 45.6 g; tlc Rf 0.45 (1:3 ethyl acetate:hexane); ^{1}H-nmr ($CDCl_3$) delta: 0.9 to 2.3 (m), which includes t-butyl singlet at 1.4, 3.0-4.8 (m), 4.9-5.2 (d), 9.6 (s).

EXAMPLE 2

Ethyl 4RS, 5S-6-Cyclohexyl-5-(t-butoxycarbonylamino)-4-hydroxy-2-hexynoate

Dry freshly distilled THF (117 mol) and diisopropylamine (22.0 ml., 15.8 g., 0.156 ml.) were charged to a flame dried reaction flask under N_2 and the resulting solution cooled to -30° and butyllithium (76.9 ml. of 1.6M in hexane, 0.123 mol) added over 5 minutes. The solution was then cooled to -78° and ethyl propiolate (12.5 ml., 12.1 g., 0.123 mol) added dropwise over 20 minutes, maintaining the temperature -65° to -78°. After 30 minutes at -78°, title product of the preceding Example (19.52 g., 0.0866 mol) in 35 ml. THF was added over 20 minutes, again maintaining -65° to -78°. After 2 hours, 200 ml. of 5:1 THF:acetic

acid was added to the reaction mixture, and it was allowed to warm to ambient temperature and diluted with a half volume of ether and an equal volume of 10% citric acid.

The organic layer was separated, washed sequentially with 2 x 200 ml. fresh 10% citric acid, 200 ml. of brine and 2 x 200 ml. saturated $NaHCO_3$, dried over $MgSO_4$ and stripped to a dark red oil, 38.2 g. The latter was chromatographed on a 10 cm x 42 cm column of silica gel with tlc monitoring, eluting with 5 l. of 1:9 ethyl acetate:hexane. After 1500 ml. to develop the column, 500 ml. fractions were collected. Fractions 29-37 were combined and stripped to yield title product as an oil, 15.3 g.; tlc Rf 0.44 (3:7 ethyl acetate:hexane); ^{1}H-nmr ($CDCl_3$) delta: 1.0-2.0 (m, 25H) including singlet for the t-butyl group at 1.5, 3.8-5 (m,6H).

EXAMPLE 3

4S,5S-6-Cyclohexyl-5-(t-butyloxycarbonylamino)-gamma-hexanolactone

Title product of the preceding Example (18.28 g.) and 5% $Pd/BaSO_4$ (10.97 g.) were combined with 150 ml. ethyl acetate and hydrogenated for 2 hours under 4 atmospheres pressure of hydrogen. The catalyst was recovered by filtration and the filtrate stripped to yield intermediate ethyl 4RS,5S-6-cyclohexyl-4-hydroxy-5-(t-butyloxyamino)hexanoate, 19 g. The latter was taken up in 250 ml. of 2.5% acetic acid in toluene, refluxed 2.5 to 3 hours, stripped and the residue chromatographed on a 10 cm. x 30 cm. column of silica gel, monitoring by tlc, eluting with 4 l. of 9:11 ether:hexane, 8 l. of 1:1 ether:hexane, 2 l. of 11:9 ether:hexane and finally 3 l. of 3:2 ether:hexane, collecting 28 x 400 ml. fractions, 6 x 150 ml. fractions and finally 11 x 400 ml. fractions. Fractions 17-24 were combined and co-stripped with ether to yield the predominant and desired, less polar, 4S,5S-title product as an oil, 9.13 g.; tlc Rf 0.5 (7:3 ether hexane). The more polar, 4R,5S-epimer of title product was isolated by stripping combined fractions 28-45 and crystallized by trituration with hexane, 1.77 g.; mp 101.5-103.5°.

EXAMPLE 4

2R,4S,5S- and 2S,4S,5S-6-Cyclohexyl-5-(t-butoxycarbonylamino)-2-(2-methyl-2-propenyl)-gamma-hexanolactone

Dry freshly distilled THF (30 ml.) and diisopropylamine (3.51 ml., 2.52 g., 0.0249 mol) were charged to a flame dried reaction flask under N_2, the resulting solution was cooled to -50°, butyllithium (13.9 ml. of 1.6M in hexane, 0.0222 mol) was added and the mixture further cooled to -78°. Title product of the preceding Example (2.77 g., 0.0089 mol) in 15 ml. THF was added dropwise over 10 minutes and the enolate allowed to form over a further 20 minutes at -78°, at which time 3-bromo-2-methyl-1-propene in 5ml. THF was added over 10 minutes, and the mixture stirred an additional 1 hour at -78°, quenched with 5 ml. saturated NH_4Cl, warmed to room temperature, diluted with a half volume of ether, washed 2 x 50 ml. 10% citric acid, 2 x 50 ml. saturated $NaHCO_3$ and 1 x 25 ml. brine, dried over $MgSO_4$ and stripped to an oil, 3.06 g., a mixture of the title epimers. The latter were separated by chromatography on 7 cm x 20 cm silica gel; monitoring by tlc; eluting sequentially with 2 l. of 1:9 ether:hexane, 4 l. of 3:17 ether:hexane, 2 l. of 1:4 ether:hexane, 2 l. of 1:3 ether:hexane, 2 l. of 7:13 ether:hexane and 2 l. of 1:1 ether:hexane; and collecting 125 ml. fractions. The less polar title product, having trans (2R) stereochemistry, was collected in fractions 30-48, combined and stripped to yield same as an oil, 1.17 g.; tlc Rf 0.45, (2:3 ether:hexane); ^{1}H-nmr ($CDCl_3$) delta 1.4 (s, 9H), 1.8 (s, 3H), 0.3-3.0 (m, 18H), 3.6-4.0 (m, 1H), 4.69 (s, 1H), 4.1-4.8 (m, 2H). Fractions 55-76 gave the more polar title product, also as an oil, 0.358 g., having cis (2S) stereochemistry; tlc Rf 0.36 (2:3 ether:hexane); ^{1}H-nmr identical to that of the less polar epimer.

EXAMPLE 5

2R,4S,5S- and 2S,4S,5S-6-Cyclohexyl-5-(t-butoxycarbonylamino)-2-(2-methylpropyl)-gamma-hexanolactone

The less polar title product of the preceding Example (1.17 g.) and 10% Pd/C (0.351 g.) were combined in 20 ml. ethyl acetate and hydrogenated at 4 atmospheres pressure for 2.5 hours, the catalyst recovered by filtration and the filtrate stripped to yield less polar title product (likewise having trans, i.e. 2R stereochemistry) as an oil which crystallized on standing, 1.20 g.; mp 88-93°; tlc Rf 0.65 (1:1 ether:hexane), Rf 0.73 (2:1 ethyl acetate:hexane). The other isomer, having cis (2S) stereochemistry, was obtained in like manner; tlc Rf 0.59 (1:1 ether:hexane). In subsequent Examples, which employ the present less polar

epimer of Rf 0.65 (1:1 ether:hexane), 2R stereochemistry is specified.

EXAMPLE 6

2R,4S,5S-6-Cyclohexyl-5-(t-butoxycarbonylamino-2-benzyl-gamma-hexanolactone

Under N_2, dry di(isopropyl)amine (2.48 ml., 0.0177 mol; distilled from CaH_2) in dry THF (7.4 ml., distilled from K) was cooled to 0°. Butyllithium (11.0 ml. of 1.62M in hexane, 0.0177 mol) was added dropwise over 5 minutes. After stirring 15 minutes at 0°, the mixture was cooled to -78° and the less polar 4S,5S-title product of Example 3 (2.30 g., 0.0074 mol) in 3.7 ml. dry THF added over 5 minutes. After stirring 30 minutes more at -78°, benzyl bromide (0.923 ml., 0.0078 mol) in 3.7 ml. dry THF was added dropwise over 5 minutes. After 1 hour at -78°, the reaction was quenched by the addition of 10 ml. saturated NH_4Cl, warmed to room temperature, diluted with 25 ml. ether and the layers separated. The organic layer was washed 2 x 15 ml. saturated $NaHCO_3$, dried ($MgSO_4$) and stripped to an oil (3.29 g.). The oil was chromatographed on 150 g. silica gel eluting with 2.5 liters 1:9 ethyl acetate:hexane and monitoring by tlc. Clean product fractions were combined and stripped to yield purified title product as a white oily solid, 1.46 g.; tlc Rf 0.60 (1:1 ethyl acetate:hexane). More polar starting material (0.91 g. of yellow oil about 70% pure, tlc Rf 0.4 in the same system) was also recovered from the column.

EXAMPLE 7

S-4-Methyl-2-(t-butoxycarbonylamino)pentanal

By the method of Example 1, N-(t-butoxycarbonyl)leucine methyl ester (28.0 g., 0.114 mol) was converted to present title product, 21.7 g. (88%), as a pale yellow oil; tlc Rf 0.36 (2:3 ethyl acetate:hexane); ^{1}H-nmr ($CDCl_3$) delta (90 MHz) 0.97 (d, J = 6, 6H), 1.1-1.8 (m, 3H), 1.4 (s, 9H), 3.3-5.0 (m, 2H), 9.53 (s, 1H).

EXAMPLE 8

Ethyl 4RS, 5S-7-Methyl-5-(t-butoxycarbonylamino)-4-hydroxy-2-octynoate

By the method of Example 2, except to use gradient elution with 3:17 to 1:4 ethyl acetate:hexane on chromatography, the product of the preceding Example (0.4 g., 0.048 mol(was converted to present title product, 5.45 g., tlc Rf 0.40 (3:7 ethyl acetate:hexane); ir ($CHCl_3$) 3438, 3340, 2233, 1711 cm^{-1}; ^{1}H-nmr ($CDCl_3$) delta (300 MHz) 0.97 (t, J = 7, 6H), 1.34 (t, J = 6, 3H), 1.48 (s, 9H), 1.48 (m,2H), 1.70(m, 1H), 3.3-3.4 (m, 1H), 3.81-3.96 (m, 1H), 4,28 (q, J = 7, 2H), 4.45-4.58 (m, 1H), 4.68-4.78 (m, 1H).

Anal. Calcd. for $C_{16}H_{27}NO_5$:			
Found:	C, 61.32; C, 61.38;	H, 8.68; H, 8.58;	N, 4.47 N, 4.42.

EXAMPLE 9

4S,5S-7-Methyl-5-(t-butoxycarbonylamino)-gamma-octanolactone

By the methods of Example 3, except to use gradient eluting with 2:3 to 1:0 ethyl acetate:hexane on chromatography, the product of the preceding Example was converted to the desired less polar (4S,5S)-lactone product, crystallized by trituration with hexane, 3.10 g. (78%); m.p. 76-77°; ir ($CHCl_3$) 3439, 1775, 1711 cm^{-1}; ^{1}H-nmr ($CDCl_3$) delta (300 MHz) 0.92 (d, J = 6, 6H), 1.44 (s, 9H), 1.28-1.81 (m, 3H), 2.06-2.32 (m, 2H), 2.48-2.58 (m, 2H), 3.79-3.92 (broad s, 1H), 4.42-4.58 (m, 2H).

Anal. Calcd. for $C_{14}H_{25}NO_4$:			
Found:	C, 61.97; C, 62.15;	H, 9.29; H, 9.26;	N, 5.16 N, 5.12.

The more polar (4R,5S)lactone was also isolated in the chromatography in much lower yield and crystallized by hexane trituration, 0.68 g., m.p. 113.5-116°C.

EXAMPLE 10

2R,4S,5S-7-Methyl-5-(t-butoxycarbonylamino)-2-(2-methyl-2-propenyl)-gamma-octanolactone

Method A

By the method of Example 4, the title product of the preceding Example (the less polar 4S,5S-epimer; 0.51 g., 0.0019 mol) was converted to present title product, in major portion, together with its more polar, 2S,4S,5S-epimer. The crude products (0.60 g.) were separated by chromatography on a 4.5 x 20 cm. column of silica gel, eluting with 1 l. each of 1:9, 3:17, 1:5, 1:4, 3:7 and 1:1 ether:hexane, collecting 23 ml. fractions. Fractions 51-85 gave purified title product, 0.21 g.; m.p. 128-132°; $[\alpha]_D^{30}$ -23.7° (c = 0.529, CH_3OH)

More polar 2S,4S,5S-epimer was isolated from fractions 89-120, 105 mg.; ^{1}H-nmr ($CDCl_3$) includes delta 4.8 (2s, 2H, vinyl protons) and 1.75 (s, 3H, vinyl methyl); a portion of this epimer was crystallized by slow evaporation from CH_2Cl_2:hexane, providing needle crystals, m.p. 99-101°.

Method B

To a suspension of lithium hexamethyldisilazide at - 78°C., prepared by the dropwise addition of 5.1 ml. (8.11 mmol) a 1.6M solution of n-butyllithium in hexane to 1.79 ml. (1.39 g., 8.49 mmol) of hexamethyldisilazane in 3.5 ml. of THF at 0°C., was added dropwise a solution of 1.00 g. (3.69 mmol) of 4S,5S-lactone of the preceding Example in 3 ml. of THF. At the end of the addition the mixture became clear and it was allowed to stir an additional 15 minutes at -78°C. A solution of 0.548 g. (4.06 mmol) of freshly distilled methallyl bromide in 2ml. of THF was then added dropwise over 5 minutes, and the mixture was allowed to slowly warm to -40°C. over 2 hours before being quenched with 2ml. of saturated NH_4Cl. After warming to room temperature the reaction mixture was partitioned between 30 ml. of ether and 30 ml. of 10% citric acid. The organic layer was separated and washed with 10% citric acid (3 x 30 ml.) and saturated $NaHCO_3$, dried ($MgSO_4$), and evaporated to 1.11 g. of crude mixture of cis(2S) and trans(2R). These lactones were separated on 88 g. of silica gel with an ether-hexane (1:9 to 3:7) eluant. The fractions containing the less polar trans (2S)lactone [tlc Rf 0.55 (1:1 ether:hexane)] were combined and evaporated to 0.613 g. (51%) of a white solid, m.p. 132-135°C. Minor impurities (as indicated by tlc) were removed by trituration in hexane to afford 0.562 g. (47%) of analytically pure title 2R,4S,5S-lactone, m.p. 133-135°C. Crystals suitable for X-ray analysis were prepared by slow evaporation from hexanemethylene chloride. ^{1}H-nmr ($CDCl_3$) delta (250 MHz) 0.90 (J, J = 6, 3H), 0.92 (d, J = 6, 3H), 1.42 (s, 9H), 1.70 (s, 3H), 1.92-2.15 (m, 2H), 2.26-2.39 (m, 1H), 2.57 (dd, J = 15 and 3, 1H), 2.72-2.88 (m, 1H), 3.77-3.90 (m, 1H), 4.34 (d, J = 9, 1H), 4.33-4.51 (m, 1H), 4.70 (s, 1H), 4.81 (s, 1H): ^{13}C-nmr (75 mHz) delta 21.8, 23.0, 24.7, 28.3, 30.0, 37.9, 39.5, 41.8, 51.7, 79.8, 80.7, 112.8, 141.9, 156.0, 179.3; IR ($CHCl_3$) 3439, 1768, 1712, 1654 cm^{-1}; $[\alpha]_D$ -25.0° (C = 0.5, CH_3OH). Anal. Calcd. for $C_{18}H_{31}NO_4$: C, 66.43; H, 9.60; N, 4.30. Found: C, 66.47; H, 9.59; N, 4.27. Single crystal X-ray analysis proved that the structure and stereochemical assignment of this compound was correct.

The fractions containing the more polar cis(2S) lactone (tlc Rf 0.44 1:11 ether:hexane) were combined and evaporated to 39 mg (3%) of a white solid, mp 96-98°C.; ^{1}H-nmr ($CDCl_3$) delta (250 MHz) 0.92 (d, J = 6, 6H), 1.43 (s, 9H), 1.72 (s, 3H), 2.02-2.14 (m, 1H), 2.23-2.36 (m, 1H), 2.60-2.87 (m, 2H), 3.74-3.89 (m, 1H), 4.35-4.47 (m, 2H), 4.69 (s, 1H), 4.78 (s, 1H); ^{13}nmr (75 MHz) delta 21.9, 22.0, 23.0, 24.8, 28.3, 30.7, 38.8, 38.9, 42.3, 50.1, 79.6, 80.4, 112.6, 142.0, 155.9, 178.7; IR ($CHCl_3$) 3443, 1774, 1714, 1656 cm^{-1}; $[\alpha]_D$-0.6° (C = 0.5, CH_3OH). Anal. Calcd. for $C_{18}H_{31}NO_4$: C, 66.43; H, 9.60; N, 4.30. Found: C, 66.94; H, 9.45; N, 4.27.

EXAMPLE 11

2R,4S,5S-7-Methyl-5-(t-butoxycarbonylamino)-2-(2-methylpropyl)-gamma-octanolactone

An ethyl acetate (10 ml) solution of 438 mg. (1.35 mmol) of the title lactone of the preceding Example containing 44 mg. of 10% Pd/C was hydrogenated on a Parr Shaker apparatus at 50 psi (345KPa) for 2 hours. After filtration of the catalyst and evaporation of the solvent, 437 mg. (99%) of present title product was obtained as a white solid, mp 130-131°C. ^{1}H-nmr ($CDCl_3$) delta (300 MHz) 0.84-0.97 (m, 12H), 1.41 (s, 9H), 1.86-1.96 (m, 1H), 2.30-2.42 (m, 1H), 2.56-2.68 (m, 1H), 3.76-3.89 (m, 1H), 4.35 (d, J=8, 1H), 4.45 (broad t, 1H); ^{13}C-nmr (75 Hz) delta 21.3, 21.8, 22.9, 23.0, 24.8, 26.1, 28.3, 31.0, 37.7, 40.5, 41.9, 51.7, 79.8, 80.5, 156.0, 180.3; IR ($CHCl_3$) 3439, 1769, 1713, cm^{-1}; [alpha]$_D$-32.1° (C=1.0, CH_3OH). Anal. Calcd. for $C_{18}H_{33}NO_4$: C, 66.02; H, 10.16; N, 4.28. Found: C, 66.07; H, 10.03; N, 4.05.

EXAMPLE 12

2R,4S,5S-6-Cyclohexyl-5-(t-butoxycarbonylamino)-2-(p-chlorobenzyl)-gamma-hexanolactone

By the method of Example 6, the less polar 4S,5S-product of Example 3 (2.5 g., 0.008 mol) and 4-chlorobenzyl bromide (1.81 g., 0.0088 mol) were converted to present chromatographed title product as a colorless gum, 1.91 g.; tlc Rf 0.6 (3:1 hexane:ethyl acetate) 0.7 (2:1 hexane:ethyl acetate with 1% acetic acid).

EXAMPLE 13

2R,4S,5S-6-Cyclohexyl-5-(t-butoxycarbonylamino)-2-(p-methylbenzyl)-gamma-hexanolactone

Using 5:1 hexane:ethyl acetate as eluant on chromatography, the method of Example 6 was used to convert the 4S,5S product of Example 3 (1.5 g., 0.0048 mol) and alpha-bromo-p-xylene (0.98 g., 0.0053 mol) to present title product as a white gum, 0.985 g.; tlc Rf 0.55 (2:1 hexane:ethyl acetate), 0.75 (1:1 hexane:ethyl acetate).

EXAMPLE 14

2R,4S,5S-6-Cyclohexyl-5-(t-butoxycarbonylamino)-2-(p-methoxybenzyl)-gamma-hexanolactone

By the method of Example 13, the 4S 5S-product of Example 3 (3.79 g., 0.0118 mol) and p-methoxybenzylbromide (2.61 g., 0.130 mol) were converted to chromatographed title product, as a white gum, 1.06 g.; tlc Rf 0.4 (3:1 hexane:ethyl acetate).

EXAMPLE 15

2R,4S,5S-6-Cyclohexyl-5-(t-butoxycarbonylamino)-2-(3,4-dichlorobenzyl)-gamma-hexanolactone

By the method of Example 6, using 3:1 hexane:ethyl acetate as eluant on chromatography, the 4S,5S-product of Example 3 (2.0 g., 0.0064 mol) and 3,5-dichlorobenzyl bromide (1.68 g., 0.007 mol) were converted to title product as a clear gum, 1.36 g.; tlc Rf 0.22 (3:1 hexane:ethyl acetate), 0.9 (1:2 hexane:ethyl acetate with 1% acetic acid).

EXAMPLE 16

2R,4S,5S-6-Cyclohexyl-5-(t-butoxycarbonylamino)-2-(o-chlorobenzyl)-gammahexanolactone

By the method of Example 6, using 6:1 hexane:ethyl acetate as eluant on chromatography, the 4S,5S-product of Example 3 (2.0 g., 0.0064 mol) and o-chlorobenzyl chloride (1.44 g., 0.007 mol) were converted to title product as a clear gum, 1.51 g.; tlc Rf 0.75 (3:1 hexane:ethyl acetate), 0.65 (2:1 hexane:ethyl acetate with 1% acetic acid).

EXAMPLE 17

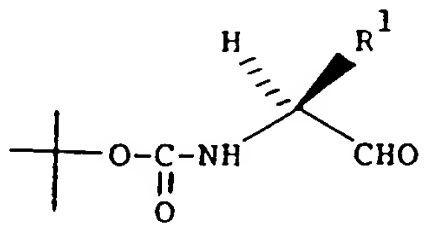
2R,4S,5S-6-Cyclohexyl-5-(t-butoxycarbonylamino)-2-(m-chlorobenzyl)-gamma-hexanolactone

By the method of the preceding Example, 4S,5S-product of Example 3 (2.0 g., 0.0064 mol) and m-chlorobenzyl chloride (0.92 ml., 1.44 g., 0.007 mol) were converted to chromatographed title product as a colorless gum, 2.11 g.; tlc Rf 0.4 (3:1 hexane:ethyl acetate), 0.75 (2:1 hexane:ethyl acetate with 1% acetic acid).

Claims

Claims for the following Contracting States : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A stereoselective process which comprises reacting an aldehyde of the formula



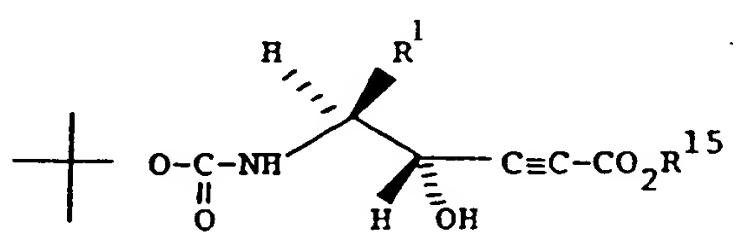
(B)

wherein R^1 is (C_1-C_6)alkyl, (C_1-C_6)alkenyl, phenyl, naphthyl, (C_4-C_7)cycloalkyl, (C_4-C_7)cycloalkenyl, (C_7-C_9)phenylalkyl, (C_{11}-C_{13})naphthylalkyl, (C_5-C_{10})(cycloalkyl)alkyl, or one of said groups mono- or disubstituted on the aromatic ring with the same or different groups selected from (C_1-C_3)alkyl, (C_1-C_3)-alkoxy, fluoro or chloro,

with $LiC{\equiv}CCOOR^{15}$,

wherein R^{15} is (C_1-C_3)alkyl,

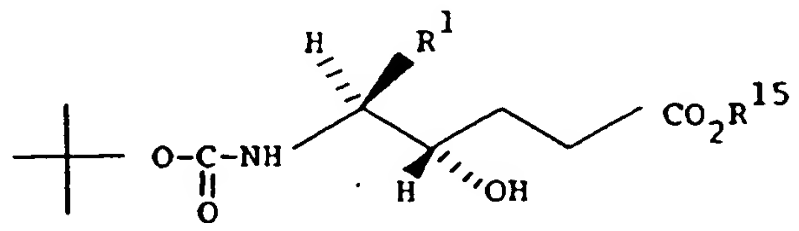
in a reaction inert solvent at -50° to -80° C. to predominantly form a compound of the formula



(C)

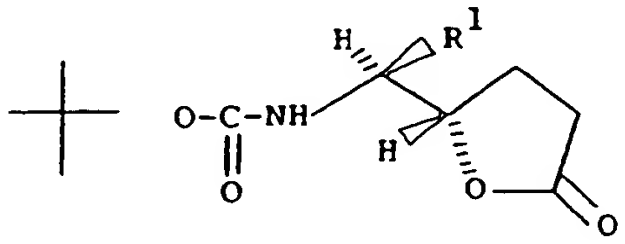
2. A process of claim 1 which further comprises the steps of:

(a) hydrogenation of the compound of the formula (C) to form a compound of the formula



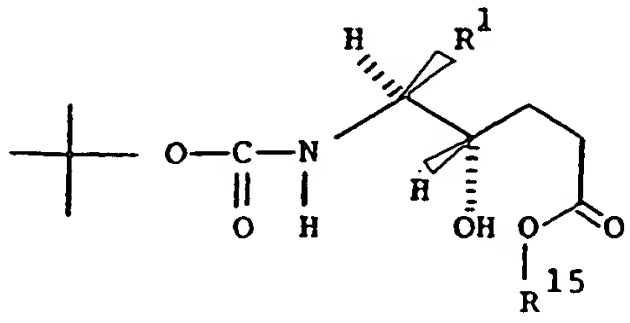
(D)

and (b) cyclization of the compound of the formula (D) to form a compound of the formula



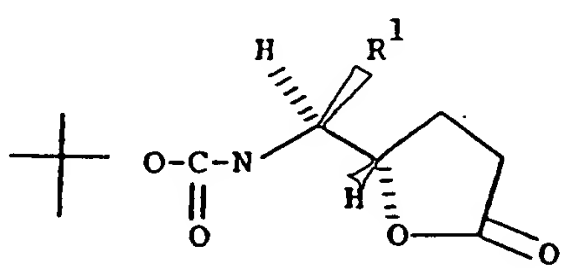
(E)

3. A compound of the formula



(III)

or

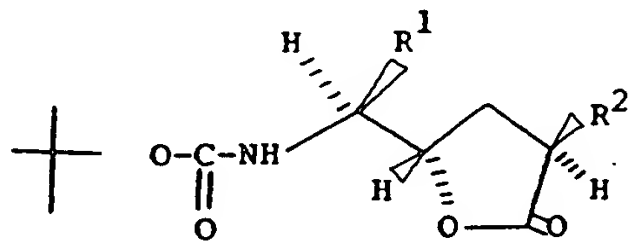


(IV)

wherein R^{15} is $(C_1\text{-}C_3)$alkyl; and

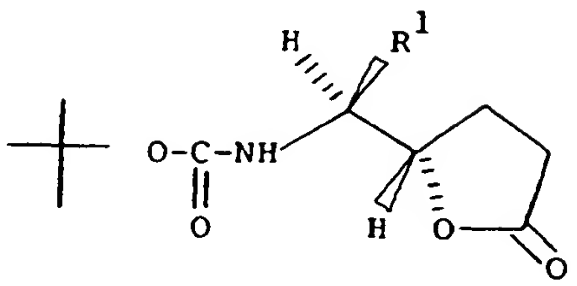
R^1 is $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkenyl, phenyl, naphthyl, $(C_4\text{-}C_7)$cycloalkyl, $(C_4\text{-}C_7)$cycloalkenyl, $(C_7\text{-}C_9)$-phenylalkyl, $(C_{11}\text{-}C_{13})$naphthylalkyl, $(C_5\text{-}C_{10})$- (cycloalkyl)alkyl, or one of said groups mono or disubstituted on the aromatic ring with the same or different groups selected from $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$-alkoxy, fluoro or chloro.

4. A stereoselective process for the preparation of a compound of the formula



wherein R^1 is $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkenyl, phenyl, naphthyl, $(C_4\text{-}C_7)$cycloalkyl, $(C_4\text{-}C_7)$cycloalkenyl, $(C_7\text{-}C_9)$phenylalkyl, $(C_{11}\text{-}C_{13})$naphthylalkyl, $(C_5\text{-}C_{10})$(cycloalkyl)alkyl, or one of said groups mono or disubstituted on an aromatic ring with the same or different substituents which are $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$alkoxy, fluoro or chloro; and R^2 is $(C_1\text{-}C_6)$(2-alkenyl), $(C_4\text{-}C_7)$(cyclo-2-alkenyl), benzyl; or naphthylmethyl or one of said groups mono- or disubstituted on an aromatic with the same or different substituents which are $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$alkoxy, fluoro or chloro;

which comprises reacting a lactone of the formula



with substantially one molar equivalent of an organic halide of the formula

R^2X

wherein X is chloro, bromo or iodo; in the presence of a substantial excess of a strong base of low nucleophilicity.

Claims for the following Contracting State : AT

1. A stereoselective process which comprises reacting an aldehyde of the formula

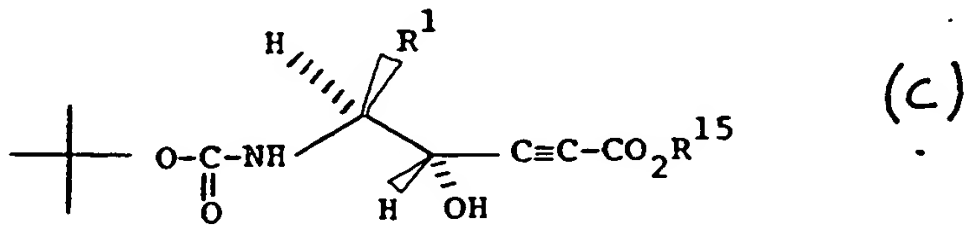
(B)

wherein R^1 is $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkenyl, phenyl, naphthyl, $(C_4\text{-}C_7)$cycloalkyl, $(C_4\text{-}C_7)$cycloalkenyl, $(C_7\text{-}C_9)$phenylalkyl, $(C_{11}\text{-}C_{13})$naphthylalkyl, $(C_5\text{-}C_{10})$(cycloalkyl)alkyl, or one of said groups mono- or disubstituted on the aromatic ring with the same or different groups selected from $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$-alkoxy, fluoro or chloro,

with $LiC{\equiv}CCOOR^{15}$,

wherein R^{15} is $(C_1\text{-}C_3)$alkyl,

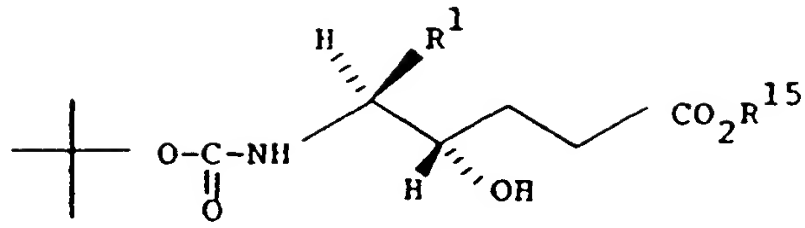
in a reaction inert solvent at -50° to -80° C. to predominantly form a compound of the formula



(C)

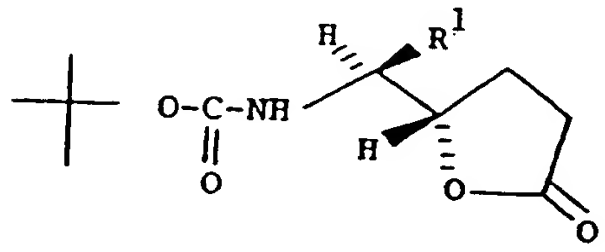
2. A process of claim 1 which further comprises the steps of:

(a) hydrogenation of the compound of the formula (C) to form a compound of the formula



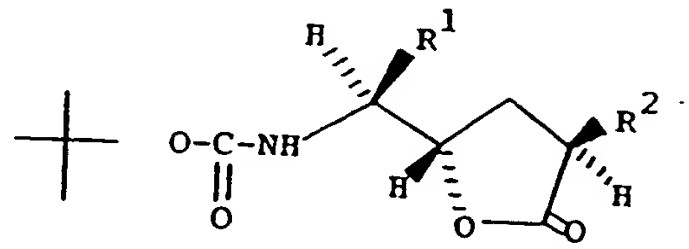
(D)

and (b) cyclization of the compound of the formula (D) to form a compound of the formula



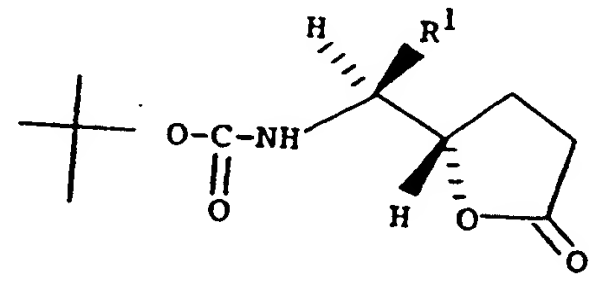
(E)

3. A stereoselective process for the preparation of a compound of the formula



wherein R^1 is $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkenyl, phenyl, naphthyl, $(C_4\text{-}C_7)$cycloalkyl, $(C_4\text{-}C_7)$cycloalkenyl, $(C_7\text{-}C_9)$phenylalkyl, $(C_{11}\text{-}C_{13})$naphthylalkyl, $(C_5\text{-}C_{10})$(cycloalkyl)alkyl, or one of said groups mono or disubstituted on the aromatic ring with the same or different substituents which are $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$alkoxy, fluoro or chloro; and R^2 is $(C_1\text{-}C_6)$(2-alkenyl), $(C_4\text{-}C_7)$(cyclo-2-alkenyl), benzyl; or naphthylmethyl or one of said groups mono- or disubstituted on an aromatic with the same or different substituents which are $(C_1\text{-}C_3)$alkyl, $(C_1\text{-}C_3)$alkoxy, fluoro or chloro;

which comprises reacting a lactone of the formula



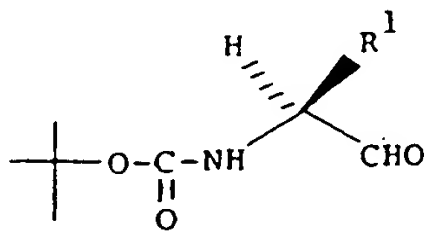
with substantially one molar equivalent of an organic halid of the formula

R^2X

wherein X is chloro, bromo or iodo; in the presence of a substantial excess of a strong base of low nucleophilicity.

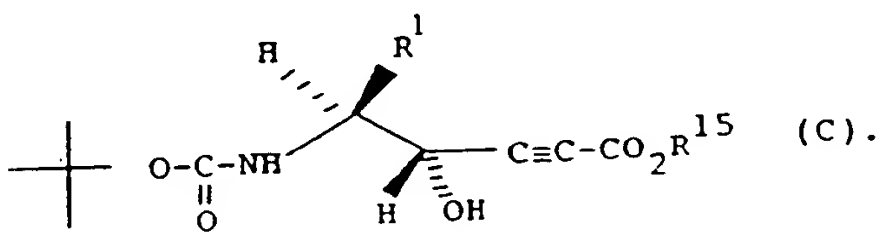
Patentansprüche
Patentansprüche für folgende Vertagsstaaten : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Stereoselektives Verfahren, das umfaßt die Umsetzung eines Aldehyds der Formel



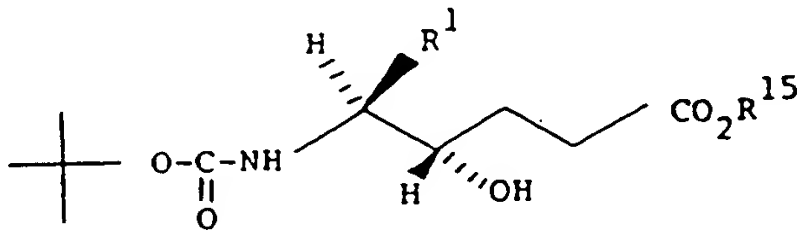
(B),

worin R^1 (C_1-C_6)Alkyl, (C_1-C_6)Alkenyl, Phenyl, Naphthyl, (C_4-C_7)Cycloalkyl, (C_4-C_7)Cycloalkenyl, (C_7-C_9)Phenylalkyl, (C_{11}-C_{13})Naphthylalkyl, (C_5-C_{10})(Cycloalkyl)alkyl oder eine dieser Gruppen bedeutet, die am aromatischen Ring mit den gleichen oder unterschiedlichen Gruppen, ausgewählt aus (C_1-C_3)-Alkyl, (C_1-C_3)Alkoxy, Fluor oder Chlor, mono- oder disubstituiert sein kann,
mit LiC≡CCOOR^{15},
worin R^{15} (C_1-C_3)Alkyl ist,
in einem reaktionsinerten Lösungsmittel bei -50 bis -80 °C zur vorherrschenden Bildung einer Verbindung der Formel



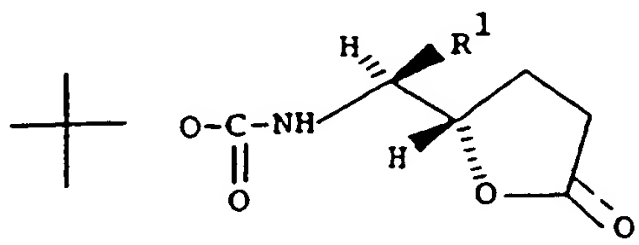
(C).

2. Verfahren nach Anspruch 1, das ferner die Schritte umfaßt:
(a) Hydrierung der Verbindung der Formel (C) zur Bildung einer Verbindung der Formel



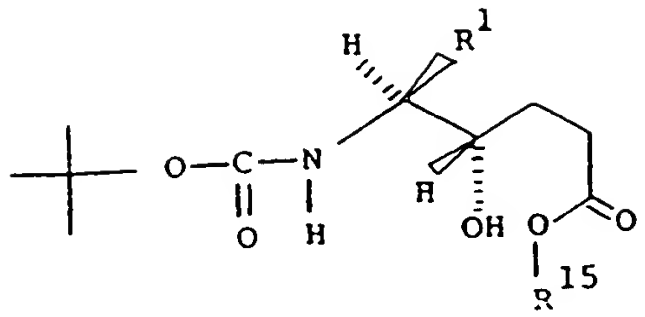
(D),

und (b) Cyclisation der Verbindung der Formel (D) zur Bildung einer Verbindung der Formel



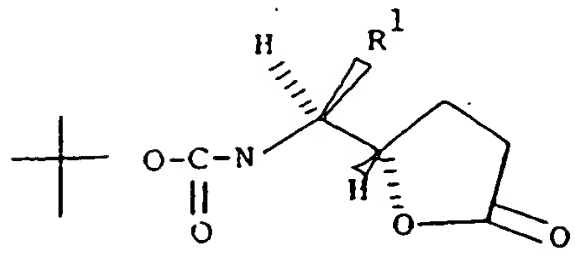
(E).

3. Verbindung der Formel



(III)

oder

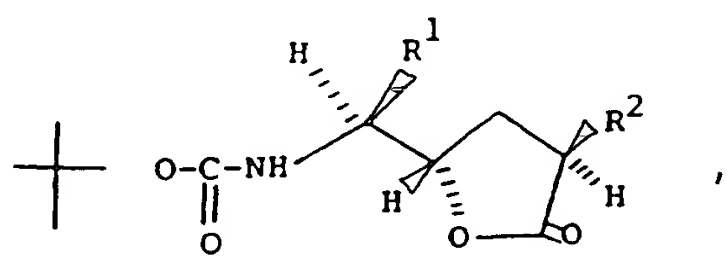


(IV),

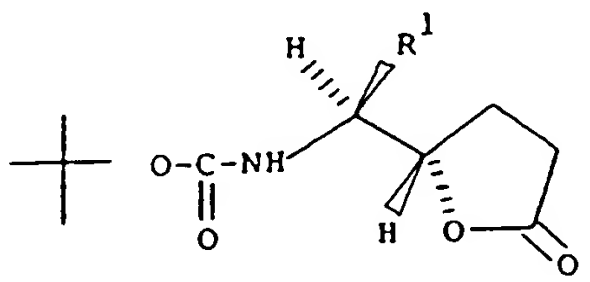
worin R^{15} (C_1-C_3)Alkyl ist und

R^1 (C_1-C_6)Alkyl, (C_1-C_6)Alkenyl, Phenyl, Naphthyl, (C_4-C_7)Cycloalkyl, (C_4-C_7)Cycloalkenyl, (C_7-C_9)-Phenylalkyl, (C_{11}-C_{13})Naphthylalkyl, (C_5-C_{10})(Cycloalkyl)alkyl oder eine dieser Gruppen bedeutet, die am aromatischen Ring mit den gleichen oder unterschiedlichen Gruppen, ausgewählt aus (C_1-C_3)Alkyl, (C_1-C_3)Alkoxy, Fluor oder Chlor, mono- oder disubstituiert sein kann.

4. Stereoselektives Verfahren zur Herstellung einer Verbindung der Formel



worin R^1 (C_1-C_6)Alkyl, (C_1-C_6)Alkenyl, Phenyl, Naphthyl, (C_4-C_7)Cycloalkyl, (C_4-C_7)Cycloalkenyl, (C_7-C_9)Phenylalkyl, (C_{11}-C_{13})Naphthylalkyl, (C_5-C_{10})(Cycloalkyl)alkyl oder eine dieser Gruppen bedeutet, die am aromatischen Ring mit den gleichen oder unterschiedlichen Gruppen, ausgewählt aus (C_1-C_3)-Alkyl, (C_1-C_3)Alkoxy, Fluor oder Chlor, mono- oder disubstituiert sein kann, und R^2 (C_1-C_6)(2-Alkenyl), (C_4-C_7)(Cyclo-2-alkenyl),Benzyl oder Naphthylmethyl oder eine dieser Gruppen bedeutet, die an einem aromatischen Ring mit den gleichen oder unterschiedlichen Substituenten, die (C_1-C_3)Alkyl, (C_1-C_3)-Alkoxy, Fluor oder Chlor sind, mono- oder disubstituiert sein kann,
das umfaßt die Umsetzung eines Lactons der Formel



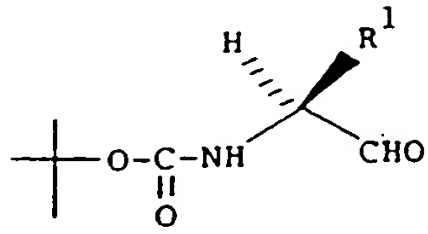
mit im wesentlichen einem Mol-Äquivalent eines organischen Halogenids der Formel

R^2X,

worin X Chlor, Brom oder Jod ist, in Gegenwart eines erheblichen Überschusses einer starken Base geringer Nukleophilität.

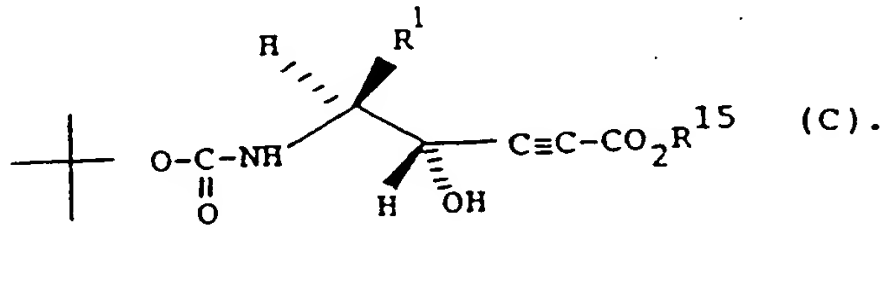
Patentansprüche für folgenden Vertragsstaat : AT

1. Stereoselektives Verfahren, das umfaßt die Umsetzung eines Aldehyds der Formel



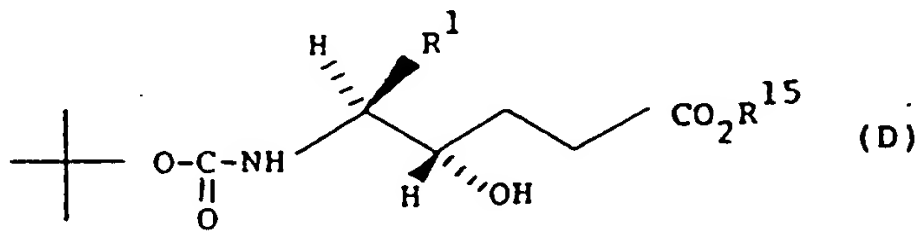
(B),

worin R^1 (C_1-C_6)Alkyl, (C_1-C_6)Alkenyl, Phenyl, Naphthyl, (C_4-C_7)Cycloalkyl, (C_4-C_7)Cycloalkenyl, (C_7-C_9)Phenylalkyl, (C_{11}-C_{13})Naphthylalkyl, (C_5-C_{10})(Cycloalkyl)alkyl oder eine dieser Gruppen bedeutet, die am aromatischen Ring mit den gleichen oder unterschiedlichen Gruppen, ausgewählt aus (C_1-C_3)-Alkyl, (C_1-C_3)Alkoxy, Fluor oder Chlor, mono- oder disubstituiert sein kann,
mit LiC≡CCOOR^{15},
worin R^{15} (C_1-C_3)Alkyl ist,
in einem reaktionsinerten Lösungsmittel bei -50 bis -80 °C zur vorherrschenden Bildung einer Verbindung der Formel



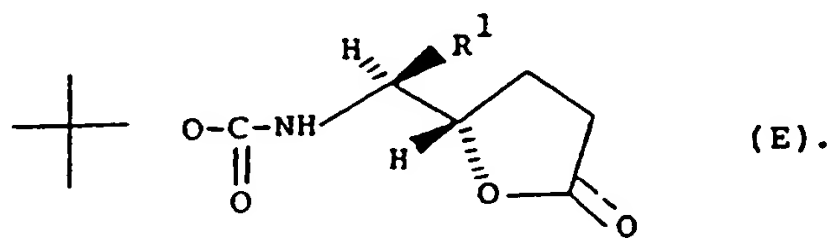
(C).

2. Verfahren nach Anspruch 1, das ferner die Schritte umfaßt:
(a) Hydrierung der Verbindung der Formel (C) zur Bildung einer Verbindung der Formel



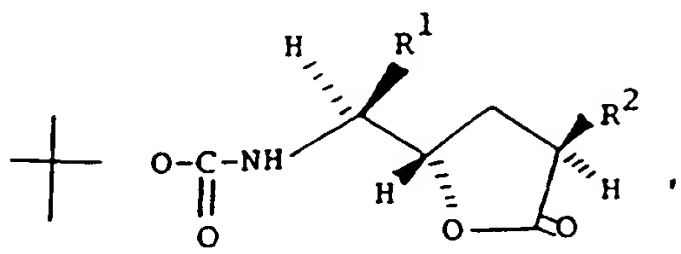
(D)

und (b) Cyclisation der Verbindung der Formel (D) zur Bildung einer Verbindung der Formel

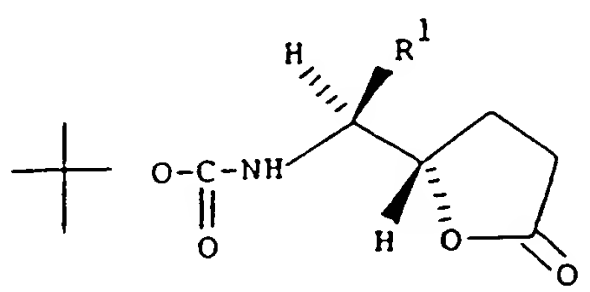


(E).

3. Stereoselektives Verfahren zur Herstellung einer Verbindung der Formel



worin R^1 (C_1-C_6)Alkyl, (C_1-C_6)Alkenyl, Phenyl, Naphthyl, (C_4-C_7)Cycloalkyl, (C_4-C_7)Cycloalkenyl, (C_7-C_9)Phenylalkyl, (C_{11}-C_{13})Naphthylalkyl, (C_5-C_{10})(Cycloalkyl)alkyl oder eine dieser Gruppen bedeutet, die am aromatischen Ring mit den gleichen oder unterschiedlichen Gruppen, die (C_1-C_3)Alkyl, (C_1-C_3)-Alkoxy, Fluor oder Chlor sind, mono- oder disubstituiert sein kann, und R^2 (C_1-C_6)(2-Alkenyl), (C_4-C_7)-(Cyclo-2-alkenyl), Benzyl oder Naphthylmethyl oder eine dieser Gruppen bedeutet, die an einem aromatischen Ring mit den gleichen oder unterschiedlichen Substituenten, die (C_1-C_3)Alkyl, (C_1-C_3)-Alkoxy, Fluor oder Chlor sind, mono- oder disubstituiert sein kann,
das umfaßt die Umsetzung eines Lactons der Formel



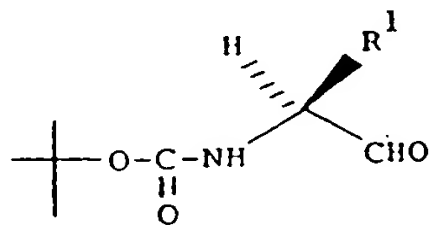
mit im wesentlichen einem Mol-Äquivalent eines organischen Halogenids der Formel

R^2X,

worin X Chlor, Brom oder Jod ist, in Gegenwart eines erheblichen Überschusses einer starken Base geringer Nukleophilität.

Revendications
Revendications pour les Etats contractants suivants : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

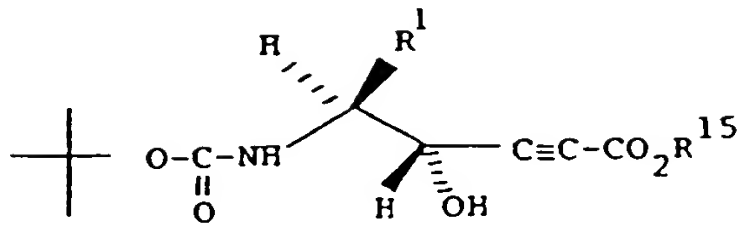
1. Procédé stéréosélectif qui consiste à faire réagir un aldéhyde de formule



(B)

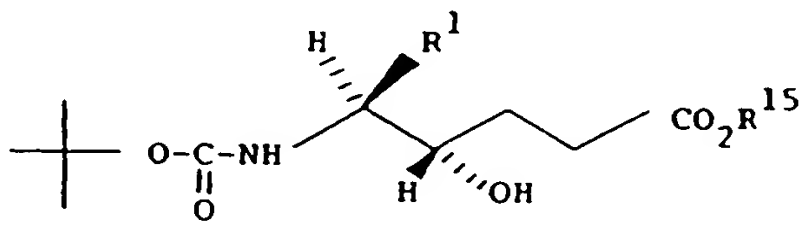
dans laquelle R^1 est un groupe alkyle en C_1 à C_6, alcényle en C_1 à C_6, phényle, naphtyle, cycloalkyle en C_4 à C_7, cycloalcényle en C_4 à C_7, phénylalkyle en C_7 à C_9, naphtylalkyle en C_{11} à C_{13}, (cycloalkyl)alkyle en C_5 à C_{10} ou bien l'un desdits groupes monosubstitués ou disubstitués sur le noyau aromatique avec les mêmes groupes ou des groupes différents choisis entre des groupes alkyle en C_1 à C_3, alkoxy en C_1 à C_3, fluoro ou chloro,
avec $LiC{\equiv}CCOOR^{15}$,
où R^{15} est un groupe alkyle en C_1 à C_3,
dans un solvant inerte vis-à-vis de la réaction entre -50 et -80 °C pour former principalement un

composé de formule



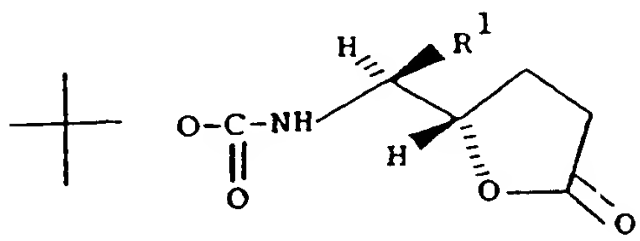
(C)

2. Procédé suivant la revendication 1, qui comprend en outre les étapes :
(a) d'hydrogénation du composé de formule (C) pour former un composé de formule :



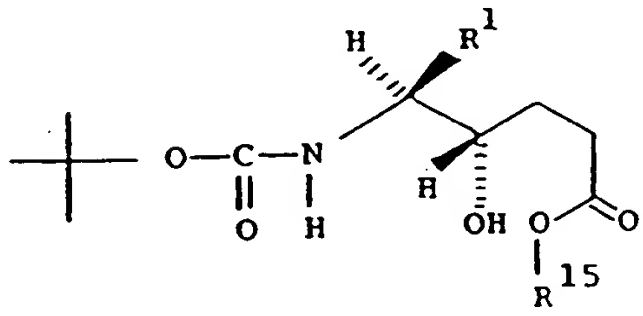
(D)

et (b) de cyclisation du composé de formule (D) pour former un composé de formule :



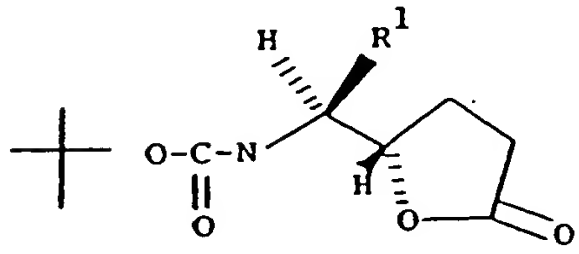
(E)

3. Composé de formule



(III)

ou

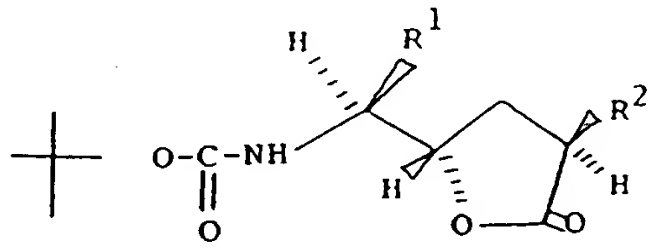


(IV)

dans laquelle R^{15} est un groupe alkyle en C_1 à C_3 ; et

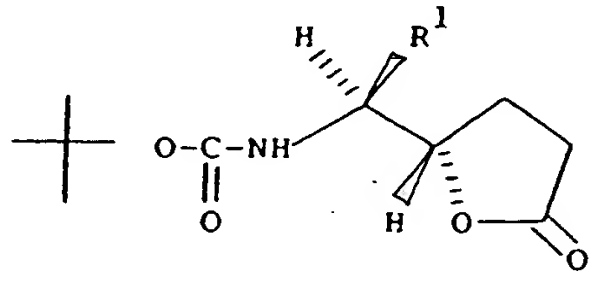
R^1 est un groupe alkyle en C_1 à C_6, alcényle en C_1 à C_6, phényle, naphtyle, cycloalkyle en C_4 à C_7, cycloalcényle en C_4 à C_7, phénylalkyle en C_7 à C_9, naphtylalkyle en C_{11} à C_{13}, (cycloalkyl)alkyle en C_5 à C_{10} ou l'un desdits groupes monosubstitués ou disubstitués sur le noyau aromatique avec les mêmes groupes ou des groupes différents choisis entre des groupes alkyle en C_1 à C_3, alkoxy en C_1 à C_3, fluoro ou chloro.

4. Procédé stéréosélectif de production d'un composé de formule



dans laquelle R^1 est un groupe alkyle en C_1 à C_6, alcényle en C_1 à C_6, phényle, naphtyle, cycloalkyle en C_4 à C_7, cycloalcényle en C_4 à C_7, phénylalkyle en C_7 à C_9, naphtylalkyle en C_{11} à C_{13}, (cycloalkyl)alkyle en C_5 à C_{10} ou bien l'un desdits groupes monosubstitués ou disubstitués sur le noyau aromatique avec les mêmes substituants ou des substituants différents qui sont des groupes alkyle en C_1 à C_3, alkoxy en C_1 à C_3, fluoro ou chloro ; et R^2 est un groupe 2-alcényle en C_1 à C_6, cyclo-2-alcényle en C_4 à C_7, benzyle ; ou un groupe naphtylméthyle ou bien l'un desdits groupes monosubstitués ou disubstitués sur un noyau aromatique avec les mêmes substituants ou des substituants différents qui sont des groupes alkyle en C_1 à C_3, alkoxy en C_1 à C_3, fluoro ou chloro ;

qui consiste à faire réagir une lactone de formule



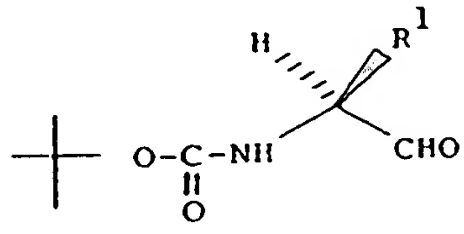
avec principalement un équivalent molaire d'un halogénure organique de formule

R^2X

dans laquelle X est un radical chloro, bromo ou iodo ; en présence d'un excès important d'une base forte faiblement nucléophile.

Revendications pour l'Etat contractant suivant : AT

1. Procédé stéréosélectif qui consiste à faire réagir un aldéhyde de formule



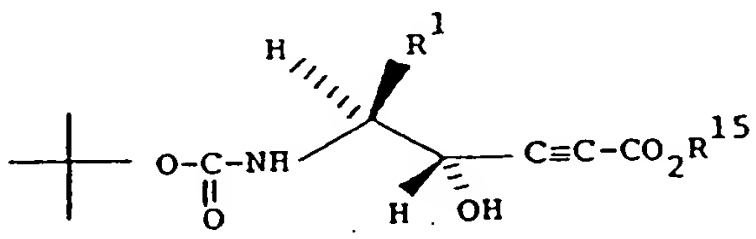
(B)

dans laquelle R^1 est un groupe alkyle en C_1 à C_6, alcényle en C_1 à C_6, phényle, naphtyle, cycloalkyle en C_4 à C_7, cycloalcényle en C_4 à C_7, phénylalkyle en C_7 à C_9, naphtylalkyle en C_{11} à C_{13}, (cycloalkyl)alkyle en C_5 à C_{10} ou bien l'un desdits groupes monosubstitués ou disubstitués sur le noyau aromatique avec les mêmes groupes ou des groupes différents choisis entre des groupes alkyle en C_1 à C_3, alkoxy en C_1 à C_3, fluoro ou chloro,

avec $LiC{\equiv}CCOOR^{15}$,

où R^{15} est un groupe alkyle en C_1 à C_3,

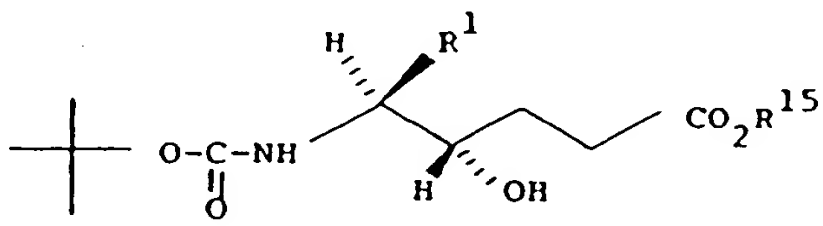
dans un solvant inerte vis-à-vis de la réaction entre -50 et -80°C pour former principalement un composé de formule



(C)

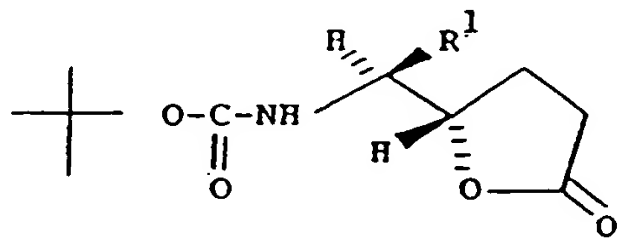
2. Procédé suivant la revendication 1, qui comprend en outre les étapes :

(a) d'hydrogénation du composé de formule (C) pour former un composé de formule :



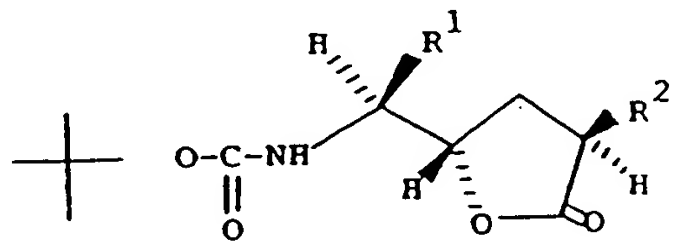
(D)

et (b) de cyclisation du composé de formule (D) pour former un composé de formule :



(E)

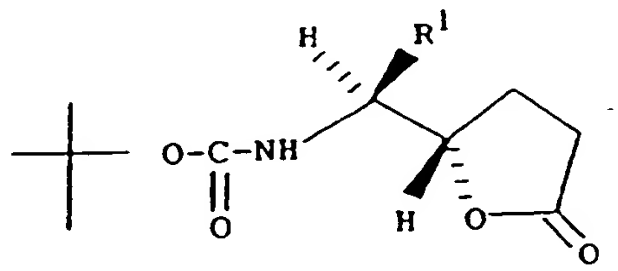
3. Procédé stéréosélectif de production d'un composé de formule



dans laquelle R^1 est un groupe alkyle en C_1 à C_6, alcényle en C_1 à C_6, phényle, naphtyle, cycloalkyle en C_4 à C_7, cycloalcényle en C_4 à C_7, phénylalkyle en C_7 à C_9, naphtylalkyle en C_{11} à C_{13}, (cycloalkyl)alkyle en C_5 à C_{10}, ou bien l'un desdits groupes monosubstitués ou disubstitués sur le noyau aromatique avec les mêmes substituants ou des substituants différents qui sont des groupes

alkyle en C_1 à C_3, alkoxy en C_1 à C_3, fluoro ou chloro ; et R^2 est un groupe 2-alcényle en C_1 à C_6, cyclo-2-alcényle en C_4 à C_7, benzyle ; ou un groupe naphtylméthyle ou bien l'un desdits groupes monosubstitués ou disubstitués sur un noyau aromatique avec les mêmes substituants ou des substituants différents qui sont des groupes alkyle en C_1 à C_3, alkoxy en C_1 à C_3, fluoro ou chloro ;

qui consiste à faire réagir une lactone de formule



avec principalement un équivalent molaire d'un halogénure organique de formule

R^2X

dans laquelle X est un radical chloro, bromo ou iodo ; en présence d'un excès important d'une base forte faiblement nucléophile.